IMPROVED ANTHELMINTIC FORMULATIONS

BACKGROUND OF INVENTION

[001] This application claims the benefit of International Application No. PCT/US2004/025005, filed August 3, 2004. The present application is a continuation-in-part of U.S. Serial No. 10/637,807, filed August 8, 2003, which is incorporated herein by reference.

[002] The invention relates generally to anthelmintic formulations which can have significant parasiticidal activity as anthelmintics, ectoparasiticides, insecticides and acaricides in animal health and more particularly to solid anthelmintic formulations containing ivermectin.

[003] Active ingredients of anthelmintics and their methods of formation in accordance with preferred embodiments of the invention are discussed in e.g. U.S. Patent Nos. 3,502,661, 4,001,411 and 4,199,569, the contents of which are incorporated herein by reference.

[004] It is often beneficial, under certain circumstances, to include multiple drugs in the same formulation in order to target a wider variety of parasites. One particularly desirable anthelmintic composition is ivermectin. Ivermectin is hygroscopic and therefore tends to be undesirably unstable. It has also been seen that ivermectin is unstable in both acidic and basic solutions and is susceptible to photodegradation and oxidative degradation. Accordingly, it is very difficult to prepare a solid composition, such as a tablet, containing ivermectin without having to resort to using a large amount of filler material to make up the bulk of the tablet in order to maintain the integrity of the compound and even then, degradation problems can exist. This problem is compounded when additional drugs are intended to be included in the same formulation, as ivermectin can degrade or be degraded other drugs.

[005] Accordingly, it is desirable to provide a multidrug anthelmintic formulation in solid form that can be formed into a solid or tablet of optimal size, palatable to animals and which can be easily administered to the affected animal.

SUMMARY OF THE INVENTION

[006] Generally speaking, in accordance with the invention, a pharmaceutical formulation is provided for use in the treatment of helminthiasis of mammals, and particularly tapeworm, hookworm, roundworm and heartworm of domestic animals and farm animals. Accordingly, the present invention provides a method of treating helminthiasis in mammals, which method comprises administering to the mammal in need thereof, an anthelmintically effective amount of a pharmaceutical formulation of the invention. The present invention also provides a composition and a method for preparing a pharmaceutical formulation containing ivermectin and a method and composition that can contain ivermectin plus other active compositions such as hexahydropyrazinoisoquinolines and anthelmintic pyrimidines such as tetrahydropyrimidines. Examples of these include, for example, praziquantel and pyrantel, respectively. Formulations in accordance with the invention can remain stable for over one month, and typically, much longer.

[007] One preferred method involves isolating the ivermectin through granulation in particular, spray granulation. The other drugs can also be granulated or spray granulated. The granules can be left in a powder form, tabletted or packed into a capsule (i.e., encapsulated). One method of preparation of the formulation comprises the following steps:

(a) preparing a first and second or a first, second and third (or more) combination including the first and second or the first, second and third active ingredient, respectively;

(b) combining the combination from (a) with dispersing agents to form two or three separate solutions;

(c) granulating one or all of the solutions, especially by spray granulation, from (b) by combining with a dry combination;

(d) drying the resulting granules, if needed;

(e) blending the granules from (d), which contain the first, second (and third) active ingredients and an excipient combination; and

(f) forming the blended granules into tablets or capsules or leaving in powder form.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[008] The present invention relates to anthelmintic active compound combinations including avermectins, hexahydropyrazinoisoquinolines and anthelmintic pyrimidines such as tetrahydropyrimidines. Acceptable tetrahydropyrimidines include, for example, pyrantel, morantel and oxantel. Acceptable hexahydropyrazinoisoquinolines include, for example, praziquantel. Other acceptable actives include benzazepines and salicylamides. Acceptable avermectins include, for example, ivermectin, doramectin, selamectin and abamectin.

[009] A formulation of active ingredients comprising ivermectin, praziquantel and pyrantel is particularly preferred. The active ingredients target different pathogenic organisms that can adversely affect the health of a mammal. This particular combination is particularly effective in fighting a wide variety of organisms. However, administering three physically separate pharmaceutical compositions to an animal is undesirable and it has been determined that it would be beneficial to combine the ingredients into one formulation, in particular one tablet (or capsule) containing a pharmaceutically effective amount of the active

ingredients, thereby decreasing the number of administrations of formulations to the animal. Thus, when the active ingredients are combined into a single formulation, the formulation provides protection against a broader spectrum of parasites than a formulation containing any parasitical agent alone. As used herein, the identification of an active ingredient, e.g., pyrantel or ivermectin, is intended to cover pharmaceutically active forms thereof such as salts, hydrochlorides, chelates, and so forth.

[0010] The formulation may also be useful in overcoming problems seen with single drug resistance. The inclusion of greater than one anthelmintic in the formulations discussed herein may have an increased likelihood of eliminating a particular helminth that is resistant to other included anthelmintic compounds. Even if the helminth is resistant to one or two of the ingredients, it is likely that at least one of the other ingredients will be effective at eliminating the helminth in question.

[0011] The disease or group of diseases described generally as helminthiasis is due to infestation of an animal host with parasitic worms known as helminths. Helminthiasis is a prevalent and serious economic problem in domesticated animals such as swine, sheep, horses, cattle, goats, dogs, cats and poultry. Among the helminths, the group of worms described as nematodes causes widespread and often times serious infection in various species of animals. Still other parasites may be located in other tissues and organs of the body such as the heart and blood vessels, subcutaneous and lymphatic tissue and the like. The parasitic infections known as helminthiases lead to anemia, malnutrition, weakness, weight loss, severe damage to the walls of the intestinal tract and other tissues and organs and, if left untreated, may result in death of the infected host.

[0012] Although the antiparasitic agents of this invention find their primary use in the treatment and/or prevention of helminthiasis, they are also useful in the prevention and treatment of diseases caused by other parasites, for example, arthropod parasites such as

ticks, lice, fleas, mites and other biting insects in domesticated animals and poultry. Repeat treatments are given as required to combat re-infestations and are dependent upon the species of parasite. The techniques for administering these materials to animals are known to those skilled in the field of veterinary medicine.

[0013] The preparations are suitable for combating pathogenic endoparasites which occur in animal husbandry and animal breeding in productive, breeding, zoo, laboratory, experimental animals and pets, and have a favorable toxicity to warm-blooded animals. In this connection, they are active against all or individual stages of development of the pests and against resistant and normally sensitive species. By combating pathogenic endoparasites, it is intended that disease, cases of death and reduction in production (for example in the production of meat, milk, wool, hides, eggs, etc.) are reduced so that more economic and simpler animal husbandry is possible by means of the use of the pharmaceutical formulation.

[0014] Productive and breeding animals include mammals, such as, for example, cattle, horses, sheep, pigs, goats, camels, water buffalo, donkeys, rabbits, fallow deer and reindeer, pelt animals, such as, for example, mink, chinchilla and raccoons, birds, such as, for example, chickens, geese, turkeys and ducks, fresh and salt-water fish, such as, for example, trout, carp and eels, and reptiles.

[0015] Laboratory and experimental animals include mice, rats, guinea pigs, golden hamsters, dogs and cats.

[0016] Pets include dogs and cats.

[0017] The formulation according to the invention is particularly preferably administered to dogs and cats, but is suitable for other mammals.

[0018] Administration can take place both prophylactically and therapeutically.

[0019] The formulations can be administered directly or in the form of suitable preparations, enterally, parenterally or dermally.

[0020] Enteral administration of the formulations takes place, for example, orally in the form of powder, tablets, capsules, pastes, potions, granules, orally administered solutions, suspensions and emulsions, boli, medicated feed or drinking water.

[0021] Suitable preparations are:

oral solutions and concentrates for oral administration after dilution;

emulsions and suspension for oral administration and semisolid preparations;

formulations in which the active compound is processed in an ointment base or in an oil-in-water or water-in-oil emulsion base;

solid preparations, such as powders, premixes or concentrates, granules, pellets, tablets, boli and capsules, with tablets the preferred form;

oral solutions are prepared by dissolving the active compound in a suitable solvent and, if appropriate, adding additives such as solubilizers, acids, bases, buffer salts, antioxidants and preservatives. The solutions are filtered and packed under sterile conditions.

[0022] Solvents may include: physiologically acceptable solvents, such as water, alcohols, such as ethanol, butanol, benzyl alcohol, methanol and isopropanol, glycerol, propylene glycol and polyethylene glycol, N-methylpyrrolidone, and mixtures of the same.

[0023] The active compounds can, if appropriate, also be dissolved in physiologically acceptable vegetable or synthetic oils.

[0024] Solubilizers may include: solvents which promote dissolution of the active compound in the main solvent or substances which prevent precipitation of the active compound. Examples are polyvinyl pyrrolidone, polyoxyethylated castor oil and polyoxyethylated sorbitan esters.

[0025] One particularly preferred formulation of the invention, comprising three active ingredients, is preferably administered in the form of capsules, more preferably tablets. A preferred formulation of the present invention contains 0.005 - 25% ivermectin, preferably 0.01 – 15%, and most preferably 0.012 – 5%, with 0.016% as a preferred example. A preferred formulation of the present invention can contain 2.0 – 58% of a secondary anthelmintic drug, such as an isoquinoline, preferably praziquantel, preferably 6 – 41%, and most preferably 11.2 – 23%, with 13.6% as a preferred example. A preferred formulation of the present invention can contain 1.5 – 76% of an anthelmintic pyrimidine, preferably pyrantel, preferably 6 – 52%, and most preferably 11.2 – 23%, with 13.6% as a preferred example. All percentages herein, unless otherwise evident, are on a weight basis.

[0026] A preferred dosage of avermectin, e.g., ivermectin, is about 5 – 7 μg/Kg body weight of the animal administered monthly, preferably 5.5 – 6.5 μg/Kg body weight, with 6 μg/Kg body weight as a preferred example. A preferred dosage of anthelmintic pyrimidines, e.g., pyrantel, is about 4.25 – 5.75 mg/Kg body weight administered monthly, preferably 4.75 – 5.25 mg/Kg, with 5 mg as a preferred example. A preferred dosage of hexahydropyrazinoisoquinaline, e.g., praziquantel, is about 4.25 – 5.75 mg/Kg body weight administered monthly, preferably 4.75 – 5.25 mg/Kg, with 5 mg as a preferred example.

[0027] To prepare solid preparations, the active compound should be mixed with suitable excipients, if appropriate, with addition of auxiliaries, and converted to the form desired.

[0028] One preferred method of preparation of the formulation comprises the following steps:

(a) preparing a first, or a first and second, or a first, second and third combination including the first, or the first and second, or the first, second and

third active ingredient, respectively, or of course, formulations involving more than three active ingredients;

(b) combining the combination from (a) with dispersing agents comprising carrier material to form one, two or three separate solutions;

(c) granulating one or all of the solutions, preferably by spray granulation, from (b)

(d) drying the resulting granules, if needed;

(e) blending the granules from (d), which contain the first, second and third active ingredients and carrier material; and

(f) if desired, forming the blended granules into tablets or filling a capsule.

[0029] The presence of acid in the formulation can decrease the stability of ivermectin. Formulations using water solvents also include citric acid, which may have an undesirable effect on ivermectin stability. Also, it is not always possible to remove all of the water in the drying step of making the formulation. The trace amount of water could accelerate the degradation of the ivermectin. To overcome these limitations the formulation may be made using a solvent such as an alcohol, instead of water, said formulation not containing citric acid. It is easier to remove such solvents, for example ethanol and isopropanol, under mild conditions.

[0030] Spray granulation involves the drying of liquid (*i.e.,* solution, suspension melt and so forth) while simultaneously building particle size. By mixing an active ingredient with a carrier in the liquid phase, the active can become "encapsulated" or substantially covered in a matrix of carrier after the spray granulation process. Granulation is generally

performed by spraying liquid into the fluidized powder. The granules are subsequently dried with heated air.

[0031] Suitable excipients may include physiologically acceptable inert solids such as, for example, sodium chloride, calcium carbonate, hydrogen carbonates, aluminum oxides, silicas, clays, precipitated or colloidal silicon dioxide and phosphates. Other suitable excipients may include, for example, sugar, cellulose, Croscarmellose Sodium, Aerosil, nutrients and feedstuffs, such as milk powder and pork liver powder, animal meals, ground and crushed cereal meals, Avicel PH102 and starches.

[0032] Auxiliaries can include preservatives, antioxidants and colorants. Additional suitable auxiliaries can include lubricants, such as, for example, magnesium stearate, stearic acid, talcum and bentonites, disintegration-promoting substances, such as starch or transversely crosslinked polyvinyl pyrrolidone, binders, such as, for example, starch, gelatin or linear polyvinyl pyrrolidone, and dry binders, such as microcrystalline cellulose.

[0033] The formulation can also be in the form of a chewable, such as a beef-chewable containing ground or minced beef or other meat, in addition to other excipients listed above.

[0034] The materials in the final formulation, such as the excipients, auxiliaries, synergists and other materials, which aid in delivery, shelf-life, desired physical structure and so forth will be referred to herein generally as carrier material. As stated herein, carrier material could be pharmaceutically active under certain circumstances.

[0035] The following examples are given for purposes of illustration only and are not intended to be construed in a limiting manner.

EXAMPLE 1: Preparation of Tablets Containing Ivermectin, Praziquantel and Pyrantel

[0036] Three separate mixtures were prepared as follows:

[0037] Mixture A:

[0038] Table 1

Ingredient	Amount (g)	% w/w
Ivermectin	8.3	0.02
Microcrystalline Cellulose USP (Avicel PH102)	2640.0	5.28
Povidone K30	2143.0	4.29
Croscarmellose Sodium	855.0	1.71
Polyethylene Glycol 8005	500.0	1.0
Citric Acid Anhydrous	10.4	0.02
Sodium Citrate Dihydrate	3.5	0.007
Purified Water	1961.5	

[0039] The ingredients were dispensed in the amounts specified in Table 1.

[0040] The following materials (in the order listed below) were passed through a Russel Sieve fitted with 20# sieve and collected in a stainless steel drum:

a) Avicel PH102

b) Croscarmellose Sodium

c) Povidone

[0041] The delumped material resulting from the step above was added to the drum tumbler and blended for 20 minutes. Purified water was added to a stock pot with citric acid and sodium citrate dihydrate. The contents were mixed for 5 minutes with a stirring rod.

[0042] Polyethylene glycol flakes were added to a separate stock pot and heated with a water bath to a temperature of 50 – 65° C to melt the flakes. The solution was maintained at this temperature. Ivermectin was added to the melted polyethylene glycol with gentle stirring until the compound was dissolved. The solution was maintained at 50 - 65° C.

[0043] 161.5g of the citrate buffer detailed above was added to the melted polyethylene glycol/ivermectin solution and stirred with gentle agitation for at least 5 minutes

until the solution was clear. The stirring was then ceased to allow any air bubbles to escape and the solution was maintained at 50 - 65° C.

[0044] The remaining citrate buffer solution was placed on a hot plate and heated to a temperature of 55 ± 5° C.

[0045] The blended Avicel, Croscarmellose Sodium and Povidone was transferred to a spray granulator. The solutions were spray granulated as follows:

a) The spray granulator was programmed with the following parameters:

1) inlet air temperature: 50 ± 10° C
2) outlet air temperature: 45 ± 10° C
3) bed temperature: 43 ± 10° C
4) atomization pressure: 3 - 5 bar
5) spray rate: 100g ± 20g per minute
6) pan speed: 2 - 10 rpm

b) The ivermectin/polyethylene glycol/citrate buffer solutions was sprayed at a rate of 100 ± 20 g/minute until all of the solution was sprayed.

c) The reserve citrate buffer at 55 ± 5° C was added to the container which held the previous solution for rinsing purposes. The rinse citrate buffer was sprayed at a rate of 100 ± 20 g/minute.

d) Granulation was continued by spraying 300g of purified water at room temperature. Additional purified water was sprayed until the desired consistency was achieved.

[0046] The granules were then emptied into the drying bowl and dried using a fluid bed drier. After drying, the bowl was removed and the granules were mixed with a scoop. The dried granules obtained were transferred in double polythene lined suitable container.

[0047] Mixture B:

[0048] Table 2:

Ingredient	Amount (g)	% w/w
Pyrantel Pamoate	19,536.0	39.07
Microcrystalline Cellulose USP (Avicel PH102)	2,285.0	4.57
Croscarmellose Sodium	810.0	1.62
Povidone K30	630.0	1.26

[0049] The ingredients were dispensed in the amounts specified in Table 2.

[0050] The following materials (in the order listed below) were passed through a Russel Sieve fitted with 20# sieve and collected in a suitable container:

a) Pyrantel Pamoate

b) Povidone

c) Croscarmellose Sodium

d) Avicel PH102

[0051] The sieved material was added to a Diosna mixer and blended for 10 minutes using the impeller on low speed with the chopper off. The mixture was granulated with 9,000g of purified water with the impeller and the chopper set on low speed. Additional purified water was added to achieve the good granular mass.

[0052] The granulated mixture was dried using a fluid bed drier and transferred to a double polythene lined suitable container.

[0053] Mixture C:

[0054]

[0055] Table 3:

Ingredient	Amount (g)	% w/w
Praziquantel USP	6,786.0	13.57
Povidone K30	715.0	1.43
Croscarmellose Sodium	835.0	1.67
Polymethacrylate USP (Eudragit E-100)	2,530.0	5.06
Citric Acid Anhydrous	789.4	1.58
Microcrystalline Cellulose USP (Avicel PH102)	1,785.0	4.57
Purified Water	See below	

[0056] The ingredients were dispensed in the amounts specified in Table 3.

[0057] The following materials (in the order listed below) were passed through a Russel Sieve fitted with 20# sieve and collected in a stainless steel drum:

a) Praziquantel USP

b) Povidone

c) Croscarmellose Sodium

d) Avicel PH102

[0058] The delumped material was mixed in a drum tumbler for 20 minutes. The mixture was added to a Diosna mixer and 10 L of purified water was gradually added with the impeller on low speed with the chopper activated for 5 minutes. The choppers were set on fast speed and run for 3 minutes. The granules were dried in a fluid bed drier and transferred to a double polythene lined suitable container.

[0059] 13,658 g of purified water was added to a stock pot and mixed with medium agitation. Citric acid and Eudragit E-100 was added to the stock pot. The mixture was stirred with medium agitation until the components had completely dissolved. The resulting Eudragit solution was allowed to settle until the air bubbles had escaped.

[0060] The praziquantel granulated mixture was added to the spray granulator and coated with the Eudragit E-100 solution. The resulting material was transferred to a double polythene lined suitable container.

[0061] Excipient Mixture:

[0062] Table 4:

Ingredient	Amount (g)	% w/w
SD Pork Liver Powder	4,048.0	8.10
Avicel PH102	1,663.0	3.33
Croscarmellose Sodium	778.0	1.58
Aerosil	150.0	0.30
Magnesium Stearate	500.0	1.00

[0063] The ingredients were dispensed in the amounts specified in Table 4.

[0064] The first four excipients were sifted through a 500# sieve and collected in a suitable container. Then the Magnesium Stearate was sifted through a 500# mesh sieve. The three mixtures containing the active ingredients of the formulation (*i.e.*, Mixtures A, B and C) and the excipient mixture were blended in a drum tumbler for 25 minutes. The sifted Magnesium Stearate was added and blended for an additional 5 minutes.

[0065] The formulation was then compressed into a plain round concave tablets of 420 mg or 840 mg and caplets of 1680 mg.

Example 2: Preparation of Tablets containing Ivermectin, Praziquantel and Pyrantel

[0066] Three separate mixtures were prepared as follows:

[0067] Mixture D:

[0068] Table 5:

Ingredient	Amount (Kg)	%w/w
Ivermectin	0.067	0.02
Avicel PH102	17.076	5.28
Povidone K30	13.861	4.29
Croscarmellose Sodium	5.530	1.71
Ethyl alcohol	12.165	NA

[0069] The ingredients were dispensed in the amounts specified in Table 5.

[0070] The following materials (in the order listed below) were passed through a Russel Sieve fitted with a 20# sieve and collected in a stainless steel drum:

a) Avicel PH102

b) Croscarmellose Sodium

c) Povidone

[0071] The delumped material resulting from the step above was added to the drum tumbler and blended for 20 minutes.

[0072] The ivermectin (0.067 Kg) was added to ethyl alcohol (1.75 Kg) with stirring and stirred until the ivermectin was dissolved. Some of the remaining ethyl alcohol (8.415 Kg) was added to the ivermectin solution.

[0073] The blended Avicel, Croscarmellose Sodium and Povidone were transferred to the spray granulator. The ivermectin solution was transferred to the designated vessel attached to the spray granulator.

[0074] The spray granulator was operated under the following conditions:

1) Inlet air temperature: $50 \pm 10^{\circ}$ C

2) Outlet air temperature: $45 \pm 10^{\circ}$ C

3) Bed temperature: $43 \pm 10^{\circ}$ C

4) Atomization pressure: 3 – 5 bar

5) Spray rate: 100 ± 20 gm per minute

6) Pan speed: 2 – 10 rpm

[0075] The ethanolic ivermectin solution was sprayed onto the dry blend (Avicel, Croscarmellose Sodium and Povidone) at a rate of 100 ± 20 gm per minute until all the solution was sprayed.

[0076] The remaining ethyl alcohol (2.0 Kg) was added to the container that had held the ethanolic ivermectin solution for rinsing purposes, and sprayed at a rate of 100 ± 20 g per minute until all the ethyl alcohol was sprayed.

[0077] Once spraying was completed, the wet mass was granulated for 10 minutes. The wet granules were then dried using a fluid bed dryer. The dried granules were transferred to a double polythene-lined container.

[0078] Mixture E:

[0079] Table 6:

Ingredient	Amount (Kg)	%w/w
Pyrantel Pamoate	126.359	39.07
Avicel PH102	14.779	4.57
Croscarmellose Sodium	5.239	1.62
Povidone K30	4.075	1.26
Isopropyl Alcohol	50.000	

[0080] The ingredients were dispensed in the amounts specified in Table 6.

[0081] The following materials (in the order listed below) were passed through a Russel Sieve fitted with a 20# sieve and collected in a suitable container:

a) Pyrantel pamoate

b) Povidone

c) Croscarmellose Sodium

d) Avicel PH102

[0082] The sieved material was added to a Diosna mixer and blended for 10 minutes using the impellor on low speed with the chopper off. The mixture was granulated with isopropyl alcohol (50.0 Kg) with the impellor and chopper set on low speeds.

[0083] The granulated mixture was dried using a fluid bed dryer and transferred to a double polythene lined container.

[0084] Mixture F:

[0085] Table 7:

Ingredient	Amount (Kg)	%w/w
Praziquantel	43.892	13.57
Avicel PH102	33.019	10.21
Povidone	4.625	1.43
Croscarmellose Sodium	5.400	1.67
Isopropyl Alcohol	28.684	

[0086] The ingredients were dispensed in the amounts specified in Table 7.

[0087] The following materials (in the order listed below) were passed through a Russel sieve fitted with a 20# sieve and collected in a stainless steel drum:

a) Praziquantel

b) Povidone

c) Croscarmellose Sodium

d) Avicel PH 102

[0088] The delumped material was transferred to a Diosna mixer and mixed for 10 minutes at slow speed with chopper off. Isopropyl alcohol (28.684 Kg) was gradually added with the impellor on low speed with the chopper activated for 5 minutes. The choppers were set on fast speed and run for 3 minutes. The granules were dried in a fluid bed dryer and transferred to a double polythene lined container.

[0089] Excipient Mixture:

[0090] Table 8:

Ingredients	Amount (Kg)	%w/w
S.D. Pork Liver Powder	26.182	8.10
Avicel PH102	10.756	3.33
Croscarmellose Sodium	8.332	2.58
Aerosil	0.970	0.30
Magnesium Stearate	3.234	1.00

[0091] The ingredients were dispensed in the amounts specified in Table 8.

[0092] The first four excipients were sifted through a 500# sieves and collected in a suitable container. Then the magnesium stearate was sifted through a 500# mesh sieve and collected in a suitable container. The three mixtures containing the active ingredients of the formulation (*i.e,* Mixtures D, E and F) and the Excipient Mixture were blended in a drum tumbler for 25 minutes. The sifted magnesium stearate was added and blended for an additional 5 minutes.

[0093] The formulation was then compressed into a plain round concave tablet of 420 mg or 840 mg and caplets of 1680 mg.

Example 3: Preparation of Tablets containing Ivermectin, Praziquantel and Pyrantel with an Eudragit E-12.5 Coating

[0094] Three separate mixtures were prepared as follows:

[0095] Mixture G:

[0096] Table 9:

Ingredient	Amount (Kg)	%w/w
Ivermectin	0.067	0.02
Avicel PH102	17.076	5.28
Povidone K30	13.861	4.29
Croscarmellose Sodium	5.530	1.71
Ethyl alcohol	12.165	

[0097] The ingredients were dispensed in the amounts specified in Table 9.

[0098] The following materials (in the order listed below) were passed through a Russel Sieve fitted with a 20# sieve and collected in a stainless steel drum:

a) Avicel PH102

b) Croscarmellose Sodium

c) Povidone

[0099] The delumped material resulting from the step above was added to the drum tumbler and blended for 20 minutes.

[00100] The ivermectin (0.067 Kg) was added to ethyl alcohol (1.75 Kg) with stirring and stirred until the ivermectin was dissolved. Some of the remaining ethyl alcohol (8.415 Kg) was added to the ivermectin solution.

[00101] The blended Avicel, Croscarmellose Sodium and Povidone were transferred to the spray granulator. The ivermectin solution was transferred to the designated vessel attached to the spray granulator.

[00102] The spray granulator was operated under the following conditions:

1) Inlet air temperature: 50 ± 10° C

2) Outlet air temperature: 45 ± 10° C

3) Bed temperature: 43 ± 10° C

4) Atomization pressure: 3 – 5 bar

5) Spray rate: 100 ± 20 g per minute

6) Pan speed: 2 – 10 rpm

[00103] The ethanolic ivermectin solution was sprayed onto the dry blend (Avicel, Croscarmellose Sodium and Povidone) at a rate of 100 ± 20 g per minute until all the solution was sprayed.

[00104] The remaining ethyl alcohol (2.0 Kg) was added to the container that had held the ethanolic ivermectin solution for rinsing purposes, and sprayed at a rate of 100 ± 20 g per minute until all the ethyl alcohol was sprayed.

[00105] Once spraying was completed, the wet mass was granulated for 10 minutes. The wet granules were then dried using a fluid bed dryer. The dried granules were transferred to a double polythene-lined container.

[00106] Mixture H:

[00107] Table 10:

Ingredient	Amount (Kg)	%w/w
Pyrantel Pamoate	126.359	39.07
Avicel PH102	14.779	4.57
Croscarmellose Sodium	5.239	1.62
Povidone K30	4.075	1.26
Isopropyl Alcohol	50.000	

[00108] The ingredients were dispensed in the amounts specified in Table 10.

[00109] The following materials (in the order listed below) were passed through a Russel Sieve fitted with a 20# sieve and collected in a suitable container:

a) Pyrantel pamoate

b) Povidone

c) Croscarmellose Sodium

d) Avicel PH102

[00110] The sieved material was added to a Diosna mixer and blended for 10 minutes using the impellor on low speed with the chopper off. Then the mixture was granulated with isopropyl alcohol (50.0 Kg) with the impellor and chopper set on low speeds.

[00111] The granulated mixture was dried using a fluid bed dryer and transferred to a double polythene lined container.

[00112] Mixture I:

[00113] Table 11:

Ingredient	Amount (Kg)	%w/w
Praziquantel	43.892	13.57
Avicel PH102	33.019	10.21
Povidone	4.625	1.43
Croscarmellose Sodium	5.400	1.67
Isopropyl Alcohol	28.684	

[00114] The ingredients were dispensed in the amounts specified in Table 11.

[00115] The following materials (in the order listed below) were passed through a Russel sieve fitted with a 20# sieve and collected in a stainless steel drum:

a) Praziquantel

b) Povidone

c) Croscarmellose Sodium

d) Avicel PH 102

[00116] The delumped material was transferred to a Diosna mixer and mixed for 10 minutes at slow speed with chopper off. Isopropyl alcohol (28.684 Kg) was gradually added with the impellor on low speed with the chopper activated for 5 minutes. Then the choppers were set on fast speed and run for 3 minutes. The granules were dried in a fluid bed dryer and transferred to a double polythene lined container.

[00117] The praziquantel granulated mixture was added to the spray granulator and coated with Eudragit E-12.5 solution (20,240 g). The resulting material was transferred to a double polythene lined container.

[00118] Excipient Mixture:

[00119] Table 12:

Ingredients	Amount (Kg)	%w/w
S.D. Pork Liver Powder	26.182	8.10
Avicel PH102	10.756	3.33
Croscarmellose Sodium	8.332	2.58
Aerosil	0.970	0.30
Magnesium Stearate	3.234	1.00

[00120] The ingredients were dispensed in the amounts specified in Table 12.

[00121] The first four excipients were sifted through a 500# sieves and collected in a suitable container. Then the magnesium stearate was sifted through a 500# mesh sieve and collected in a suitable container. The three mixtures containing the active ingredients of the formulation (*i.e,* Mixtures G, H and I) and the Excipient Mixture were blended in a drum tumbler for 25 minutes. The sifted magnesium stearate was added and blended for an additional 5 minutes.

[00122] The formulation was then compressed into a plain round concave tablet of 420 mg or 840 mg and caplets of 1680 mg.

[00123] It will thus be seen that the objects set forth above, among those made apparent from the preceding description, are efficiently attained and, since certain changes may be made in carrying out the above method and in the composition set forth without departing from the spirit and scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

[00124] It is also to be understood that the following claims are intended to cover all of the generic and specific features of the invention herein described and all statements of the scope of the invention which, as a matter of language, might be said to fall therebetween. Particularly it is to be understood that in said claims, ingredients or compounds recited in the singular are intended to include compatible mixtures of such ingredients wherever the sense permits.